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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,644	07/13/2001	Daniel Vanna Siev	018813/027 2492	2686

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EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT PAPER NUMBER

1624

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/905,644

Applicant(s)

SIEV ET AL.

Examiner

Venkataraman Balasubramanian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-8,10-12,14,15,18-23,25-29 and 33-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,3-23,25-29,33 and 50-57 is/are allowed.
- 6) ☒ Claim(s) 34-49 and 58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, which included cancellation of claims 2, 24, addition of new claims 57-58 and amendment to claims 1, 3, 14, 25-26, 35, 43, filed on 6/13/2003, is made of record.

Claims 1, 3-8, 10-12, 14-15, 18-23, 25-29, 33-58 are now pending.

In view of applicants' response, the following apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-49 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of thrombosis, does not reasonably provide enablement for treating or decreasing the incidence of any or all conditions generically embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record. To repeat:

The instant pharmaceutical composition claims 34-41 reciting intended use and method of use 42-49 and 58 are drawn to 'treating or decreasing the incidence of a condition characterized by abnormal thrombosis. The scope of the claims includes not only treatment but also decreasing the incidence of thrombosis which is not adequately enabled solely based on the activity of the compounds provided in the specification at

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pages 1-13, 42-53. The instant compounds are disclosed thrombin inhibitory activity and it is recited that the instant compounds are useful in 'treating or decreasing the incidence of several conditions, for which applicants provide no competent evidence. "To decrease the incidence of abnormal thrombosis" means actually means to *anticipate abnormal thrombosis and or counter in advance, to keep from happening etc.* and there is no disclosure as to how one skilled in the art can reasonably establish the basis anticipation for abnormal thrombosis and the type of subject to which the instant compounds can be administered in order to have the "decreasing incidence" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the abnormal thrombosis claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'decreasing incidence' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rauch et al., (PubMed Abstract enclosed) wherein with regards to antithrombotic therapies, it is stated that "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al., (PubMed Abstract enclosed) with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors

have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

- 1) The nature of the invention: Therapeutic use of the compounds in treating and or decreasing the incidence of abnormal thrombosis that require thrombin inhibitory activity.
- 2) The state of the prior art: A very recent publication expressed that the pharmacokinetics and anticoagulant effects of thrombin inhibitors are unpredictable.
- 3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the 'preventive' effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
- 4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show decreasing the

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incidence effect and the state of the art is that the effects of thrombin inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace not only treatment but also the decreasing the incidence of any or all conditions characterized by abnormal thrombosis

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards 'decreasing the incidence of the variety of conditions generically embraced, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Applicants should note that this rejection is same as made in the previous office action except that newly added claim 58 is now included in the rejection.

Applicants' argument to overcome this rejection is not persuasive.

First of all, applicants should note that this rejection is a scope of enablement rejection. The issue is scope of enablement of "treating or decreasing the incidence of a condition in mammal characterized by abnormal thrombosis" .The scope of the claims

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includes not only any or all conditions but also those condition yet to be discovered as due to "abnormal thrombosis" for which there is no enabling disclosure. Furthermore, applicants have not offered a clear-cut definition of "abnormal thrombosis" and "conditions as characterized by "abnormal thrombosis". As for the claim language "decreasing the incidence", applicants assert that it is not prevention, but have not stated what it is meant to be, particularly in context of "abnormal thrombosis".

Applicants have cited some US patents to support their position but applicants should note that each applications is examine case by case. Furthermore, applicants have not shown wherein these US Patents, support for "treating or decreasing the incidence of a condition in mammal characterized by abnormal thrombosis" is provided.

Again, it is not clear how would one know the difference between "abnormal thrombosis" and normal thrombosis, how would one distinguish between conditions mediated by abnormal thrombosis and normal thrombosis, how would one know who is prone to the incidence of "abnormal thrombosis" and how would one selectively "decrease the incidence of abnormal thrombosis" without affecting thrombosis. As noted above, decrease the incidence of abnormal thrombosis contrary to applicants' urging is prevention and newly added claim 58 clearly recites "preventing" abnormal thrombosis.

As for Rauch et al. and Van Aken et al., cited by the examiner,(now full article kindly provided by the applicants) contrary to applicants urging, these citation do not lend support to applicants contention that the instant invention is enabled for all or any condition characterized by abnormal thrombosis. They are indeed limited to treating

thrombosis. Careful reading suggests that the studies are still exploratory and need further experimentation.

See Rauch et al., wherein with regards to antithrombotic therapies, it is stated, "Current antithrombotic therapies available as long-term treatment for patients with cardiovascular disease are often not effective enough to prevent acute thrombotic events and deterioration of atherosclerosis". Also, Van Aken et al with regards to therapeutic approach of thromboembolic disorders, expresses that 'thrombin inhibitors have limitations because their pharmacokinetics and anticoagulant effects are unpredictable'. In addition, based on the claim language, it appears that applicant's compounds are effective for "abnormal thrombosis". Specification has no teaching as to this as assays relied upon are for thrombin or related factor inhibition.

Hence the rejection is proper and is maintained.

Allowable Subject Matter

Claims 1,3-23, 25-29, 33, 50-57 would be allowable. The said claims would be allowed since specific species and composition embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.


Venkataraman Balasubramanian

8/27/2003